By the morning of May 26 the patient was able to open her mouth a little wider. At 11 p.m. she was found to be perspiring freely, the respiration was gasping in character, and her muscles were extremely relaxed, so the drip was stopped, and by 1 a.m. she was quite comfortable. The next morning she was breathing without difficulty and no sign of muscle spasm remained : she was alert after a very restful night. No further gallamine was required. On May 28 she was able to eat solid food. Although muscle tone remained increased, no further spasms occurred. Respiratory infection resolved rapidly, the low-grade pyrexia ended on May 30, and her general condition steadily improved. The anaemia did not respond to oral iron, and an iron-absorption test showed no absorption. A course of "ferrivenin" totalling 1.47 g. was given, raising the haemoglobin to 82% (12.1 g.).

Over the 11½ days of continuous administration 3,710 mg. of gallamine triethiodide was administered (see Chart). At no time was an oxygen tent or artificial respirator required.

Summary

A case of tetanus is described which began about two weeks after a minor injury to a thumb that had become septic. At the time of admission trismus and hypertonus were present. By the eighth day of the disease it was obvious that the increased frequency and severity of the tetanic spasms would not respond to normal sedation with barbiturates and morphine, and it was decided to try the effect of gallamine. At first this was administered intramuscularly, but three-hourly injections proved insufficient to control spasms. Hourly injections into the rubber tubing of a saline intravenous drip were found to be satisfactory, as was administration hourly into a subcutaneous hyaluronidase infusion.

As the days passed it became noticeable that steadily increasing amounts of gallamine were required to prevent spasms ; in view of this, the sudden termination of the tetanic spasms was quite unexpected. Morphine sulphate, ¼ gr. (16 mg.), and amylobarbitone sodium, 3 gr. (0.2 g.), were administered each evening and at other times as required.

We wish to thank Drs. Sheila Watts and Pamela J. Houchin for their continuous and untiring help in the supervision and treatment of this patient. We gratefully acknowledge the information provided by the Medical Information Division of Pharmaceutical Specialities (May & Baker) Ltd. and used in the preparation of this paper.

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At the anniversary meeting of the Royal Society on December 1 Dr. E. D. Adrian, in his presidential address, paid a special tribute to Sir Charles Sherrington, who died last March at the age of 94. He had been president of the Royal Society from 1920 to 1925. In Dr. Adrian's words, "few scientists of our time have been so well qualified to judge the advance of human understanding of the natural world, for he lived long enough to have witnessed most of the great achievements of the present era, and he had made an intimate study of the science of the Middle Ages, when the schoolmen and alchemists were as satisfied with their theories as we are with ours."

PROLONGED WOUND ANALGESIA AFTER SURGICAL OPERATIONS

CLINICAL TRIAL OF EFOCAINE

BY

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Post-operative pain is an almost universal sequel to every type of surgical procedure and, apart from causing distress to the individual patient, contributes to a number of secondary complications such as inhibition of the cough reflex and consequent pulmonary collapse, retention of urine, delayed mobilization leading to venous stasis and thrombosis, loss of sleep, and delayed convalescence.

The aqueous solutions of local analgesics hitherto in use have suffered from the disadvantage of rapid diffusion and elimination from the area of infiltration, so that even with the addition of adrenaline the effect is unlikely to last for more than four hours. Oily solutions such as "proctocaine" and benzocaine compound injection *N.F.* (A.B.A.) have been inconsistent in their action, and have caused trouble from abscess formation and local necrosis.

American workers (Iason and Shaftel, 1952a, 1952b ; Puderbach and Shaftel, 1952 ; Raicus, 1952 ; Weinberg, 1952) have recently described a new product marketed under the name of "efocaine," composed of procaine base 1%, with procaine hydrochloride 0.25%, and butyl *p*-aminobenzoate 5% in propylene glycol 78% and polyethylene glycol 300 2%. This clear solution is non-oily, though somewhat .viscous, and is freely miscible with body fluids ; none of the constituents appear to have any toxic effects. The solution is saturated, but on contact with the body fluids the local analgesic is immediately precipitated in a relatively insoluble form which exerts an effect for from 8 to 20 days.

Clinical Trial

In order to obtain experience of the use of this product and to assess its therapeutic possibilities, a series of patients were selected who were undergoing the commoner operations in which post-operative pain usually necessitates the administration of analgesic drugs. The first two cases were elective appendicectomies performed through McBurney incisions. At the conclusion of the operation, before peritoneal closure, the solution was introduced into the intermuscular plane above and lateral to the incision, 5–6 ml. being used. The wounds were insensitive for the whole of the patient's stay in hospital (eight days), but both patients complained of intestinal discomfort for the usual 36 hours.

Having established that prolonged analgesia of a small wound could be obtained, a regional block of T 11 and 12 and L 1 (2 ml. each nerve) was then attempted in a nephroureterectomy for renal tuberculosis, with a right paramedian as well as a lumbar incision. Here there was a good deal of pelvic dissection, which resulted in abdominal discomfort. Complete analgesia was not achieved, but the lumbar incision remained partly anaesthetic for 20 days. A similar lumbar block of T. 11 and 12 and L. 1 was performed on a patient after left lumbar ganglionectomy by the anterolateral route. There was no post-operative pain and the scar was only slightly sensitive on the twelfth day.

Three inguinal hernia patients were given 10–12 ml. of the solution, partly into the intermuscular plane near the iliac

Case	Sex and Age	Operation	Method of Administration	Effects	Comment
1	F 25	Interim appendicectomy	6 ml. infiltrated into intermuscular plane lateral to wound	Intestinal discomfort 36 hours. Anaesthesia of wound for 7 days +	Good
2	F 12	Appendicectomy and removal of fimbrial cyst	5 ml. infiltrated (as above)	Abdominal discomfort 24 hours. Anaesthesia of wound for 8 days +	,,
3	F 23	Nephro-ureterectomy for renal tuberculosis	Regional block T. 11, 12, L. 1 (2 ml. each nerve)	Partial analgesia of wound for 20 days. Abdominal discomfort 3–4 days	Fair
4	M 55	Perforated duodenal ulcer	7 ml. into rectus sheath and subcutaneous tissue on each side	No apparent effect	Failed
5	M 35	Haemorrhoidectomy (St. Mark's)	10 ml. round inferior haemorrhoidal nerve and into sphincters	Painless convalescence. Anal anaesthesia for 10 days and slight retention of urine	Good
6	M 57	Vagotomy and gastroenterostomy	10 ml. into right intercostal block, T. 7–11, also into left rectus sheath	Slight wound discomfort on coughing. Sensation back to normal in 6 days	Fair
7	M 60	Vagotomy and gastroenterostomy	20 ml. given as bilateral intercostal block T. 7–11	No post-operative pain. Slight discomfort on coughing. Wound insensitive 10 days +	Good
8	M 62	Abdominal vagotomy	20 ml. given as bilateral intercostal block T. 7–11	No post-operative pain. Wound anaesthesia 7 days +	,,
9	M 68	Left antero-lateral lumbar ganglionectomy	6 ml. regional block T. 11, 12, L. 1 (2 ml. each nerve)	No post-operative pain. Scar remained slightly sensitive	Fair
10	F 55	Right inguinal hernia	Local intermuscular and subcutaneous infiltration	No apparent effect	Failed (obese patient)
11	M 40	,, ,, ,,	12 ml. by local infiltration and round L. 1 near iliac spine	Slight wound haematoma. No definite anaesthesia	Failed
12	M 42	Partial gastrectomy	18 ml. bilateral intercostal block T. 7–12	No post-operative wound pain even on coughing. Skin anaesthesia not definite	Good
13	M 47	Haemorrhoidectomy (St. Mark's)	10 ml. round inferior haemorrhoidal nerve and sphincters	No post-operative pain (5 days)	,,
14	M 42	Left inguinal hernia	10 ml. infiltrated in intermuscular plane round ilio-hypogastric nerve and subcutaneously	Complete analgesia 5 days +. Haematoma	,,

spine so as to block the ilio-hypogastric and ilio-inguinal nerves, and partly subcutaneously to desensitize the skin incision. The first case was an obese woman with a direct hernia, and was unsuccessful, presumably owing to difficulty in accurate placing of the analgesic and its dissipation in the subcutaneous fat. In the second there was little post-operative pain, though actual skin anaesthesia was not achieved; in the third there was complete abolition of both post-operative pain and wound sensitiveness.

Two patients subjected to haemorrhoidectomy by the St. Mark's technique received, at the conclusion of the operation, 10 ml. of efocaine, 2.5 ml. being injected round each inferior haemorrhoidal nerve and about 5 ml. round the subcutaneous sphincter. Complete abolition of pain was achieved and neither patient required post-operative sedation. The first patient, nevertheless, had slight difficulty in micturition for 24 hours, and later commented that he had difficulty in knowing whether he was defaecating or not, owing to the loss of anal sensation, which persisted for at least 10 days. The second patient is analgesic at the time of writing (five days).

Five patients subjected to upper abdominal incisions for gastric surgery were also treated. The first, a chronic bronchitic with perforation of a duodenal ulcer, received at the conclusion of the operation a total of 7 ml. of efocaine, injected into the rectus sheath and subcutaneously on each side of the wound. There was no definite effect. When more ample supplies of efocaine became available the four other patients were treated by anterior intercostal block: from 1–2 ml. was used in each space, and the seventh to the eleventh nerves were injected. One patient experienced slight discomfort on coughing and sneezing, and sensation had returned to normal in six days; he had received only 10 ml. of efocaine by right-sided intercostal block (T. 7–11) and infiltration of the left rectus sheath. In the remaining three patients rectus sheath infiltration was discarded, 18–20 ml. of efocaine being used exclusively for a bilateral intercostal block. Their wounds were painless for at least seven days, though the loss of actual sensation was patchy. In particular, one man, seen five hours after partial gastrectomy, was sitting up cheerfully in bed maintaining that he had no pain at all; his wound could be handled vigorously without causing discomfort, and he coughed strongly without distress: this did not, however, prevent him from developing post-operative bronchitis.

Difficulties

The relative viscosity of the solution to be injected necessitates the use of a locking syringe if a narrow-gauge needle is to be used, as otherwise the force required to inject the solution is likely to detach the needle and waste the solution. Wide-bore needles have a tendency to cause haematomata (two instances), though these have given no serious trouble.

The low diffusibility of the solution means that to be effective it must be deposited in close proximity to the nerve to be blocked. Wide infiltration of the wound area itself is unreliable, particularly in obese patients, owing to dissipation of the analgesic. The results have been far more consistent when accurate nerve-blocking was possible—for example, antero-lateral intercostal, or inferior haemorrhoidal. In some cases the impression was that the analgesia did not become maximal until after 48 hours.

Desensitization of a wound does not abolish pain due to visceral distension.

According to the American literature the injection of efocaine produces a burning pain, especially if too near the skin. All our patients have received injection while under general anaesthesia, and we have therefore no comment to make on this point.

Summary and Conclusion

The claim that efocaine can produce prolonged analgesia of an operation wound has been substantiated. Of 14 patients, a good result was obtained in 8, a fair result in 3, and there was no apparent effect in 3.

To be effective an adequate concentration must be deposited in close proximity to the nerves supplying the area: an accurate nerve block is therefore more efficient than local infiltration of the area.

By its means, analgesia of a wound for periods of from 8 to 20 days can be achieved.

The viscous solution should be used with a locking syringe and the needle kept moving to avoid depot formation. A wide-bore needle may lead to wound haematoma.

No undesirable effects have been observed; on the contrary, the atmosphere in a ward with several recent

operation cases was unusually cheerful and the need for post-operative drugs was much reduced.

The method would appear to be of value in controlling pain following operations on the chest, upper abdomen, loin, and ano-rectal region : it may also prove of value in the treatment of fractured ribs. It would appear to be less effective when obesity makes accurate placing of the solution difficult, and is contra-indicated in the presence of infection.

On theoretical grounds one would expect a reduction in secondary complications due to inhibition of the cough reflex and retention of urine, but our series is too small for the forming of any conclusions on this point.

I am indebted to my colleague Dr. James Rochford and to Messrs. Crookes Laboratories for supplies of efocaine and for helpful advice on the methods of use.

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COLLAGEN/CHONDROITIN SULPHATE RATIO OF HUMAN ARTICULAR CARTILAGE RELATED TO FUNCTION

BY

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In a study of the physical and biochemical changes which accompany the ageing of hyaline articular cartilage a preliminary examination of the two main components, collagen and chondroitin sulphate, showed a very different ratio in some joints compared with others. This is, I suggest, related to mechanical function, since weight-bearing and non-weight-bearing areas of articular cartilage differ significantly in collagen and chondroitin sulphate content, whether comparison is made between joints or between different areas within the same joint.

Material and Methods

The material was taken within one hour of necropsy from adult patients whose articular cartilage showed no macroscopic evidence of senile change. Slices about 1 mm. thick were removed from the whole of the articular surface of the head of the humerus and the lower end of the homolateral femur: an aliquot was taken for analysis.

For comparison of weight-bearing and non-weight-bearing areas within an individual knee-joint, slices were taken from the following sites: (*a*) patellar surface of the femur, (*b*) the middle (weight-bearing) thirds of both femoral condyles, and (*c*) the posterior (non-weight-bearing) thirds of both condyles. These samples were compared with cartilage from (*d*) the centre of the medial surface (non-weight-bearing) of the humeral head, and from (*e*) the superior (weight-bearing) surface of the head of the femur.

The cartilage slices were dried in acetone and then over sulphuric acid to constant weight. Determination of the hydroxyproline content was made according to the method of Neuman and Logan (1950a), and collagen values were obtained by multiplying the hydroxyproline figures by 7.5 (Neuman and Logan, 1950b).

Chondroitin sulphate was determined by estimation of hexosamine after hydrolysis according to the method of Elson and Morgan (1933). The factor for conversion of hexosamine to chondroitin sulphate is approximately 4 (Einbinder and Schubert, 1950).

Results

Table I gives the results of five typical estimations. It is evident that the chondroitin sulphate content of knee cartilage is greater than that of the shoulder, but that the reverse holds for collagen.

TABLE I.—*Collagen and Chondroitin Sulphate Content of Healthy Articular Cartilage: Comparison of Knee and Shoulder (% of Dry Weight)*

Case	Age	Collagen		Chondroitin Sulphate		Collagen/ Chondroitin Sulphate Ratio	
		Knee	Shoulder	Knee	Shoulder	Knee	Shoulder
1	38	66·0	75·0	22·4	14·4	2·9	5·2
2	49	52·5	69·8	20·8	16·4	2·5	4·3
3	55	63·0	74·3	22·8	17·2	2·8	4·3
4	60	59·3	67·5	19·6	14·8	3·0	4·6
5	66	51·0	69·8	22·0	15·6	2·3	4·5

Table II shows that if comparison be made between joints (or between different areas within the same joint) the content of chondroitin sulphate is greater and the collagen less in weight-bearing articular cartilage than in cartilage which bears no weight.

TABLE II.—*Collagen and Chondroitin Sulphate Content of Weight-bearing and Non-weight-bearing Articular Cartilage (% of Dry Weight) in Man Aged 55*

Joint	Site	Collagen	Chondroitin Sulphate	Collagen/ Chondroitin Sulphate Ratio
Weight-bearing: Knee (articular surface of femur)	Medial condyle (middle third)	47·3	24·8	1·9
	Lateral condyle (middle third)	50·3	24·0	2·1
	Patellar surface	49·5	23·6	2·1
Hip ..	Head of femur	50·3	23·6	2·1
Non-weight bearing: Knee (articular surface of femur)	Medial condyle (posterior third)	57·8	18·8	3·1
	Lateral condyle (posterior third)	59·3	16·0	3·7
Shoulder ..	Head of humerus	66·0	16·8	3·9

Although, strictly speaking, the patellar articular surface of the femur is not weight-bearing, it is an area subject to marked shearing action, and its composition resembles that of weight-bearing cartilage.

Discussion

The importance of mechanical function in determining the composition of articular cartilage is illustrated by the results shown above: the greater resilience needed in weight-bearing areas is provided by a higher polysaccharide content.

It is well known that the earliest degenerative changes in the knee occur on the middle third of the articular surface of the medial femoral condyle and on the femoral patellar surface. It is conceivable that the susceptibility to degeneration of weight-bearing or stressed sites is related to the special structural adaptation to function revealed by the above analysis. It is hoped in future work to test this hypothesis.

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